Introduction

Introduction

This lesson serves as an overview of the Endocrine module. It isn't meant to be a real lesson where you learn concrete information or start engaging the details. It is here to establish both the framework and patterns found in endocrinology. Endocrine is actually very easy to understand, but also very easy to get confused. Feedforward and feedback, sometimes negative and sometimes positive, allow for multiple permutations of what could be, and only one is correct for any given gland.

This first lesson doesn't have questions associated with it. We don't discuss feedback loops or give the specifics of any axis, nor do we really define what an axis is. If you do the Endocrine module in the order prescribed, you will pick up the necessary pieces as you go. Don't skip around. The module is meant to be done in order, lessons 1 through 18.

Endocrine Organs

Most of endocrinology is managed by the hypothalamic-pituitary axis.

The **hypothalamus** and **pituitary** are discussed in the first series. Although only two lessons long, it establishes the framework for the Adrenal gland and Thyroid series. Those lessons will be too complicated without first covering the hypothalamus and pituitary. The hypothalamus both makes and stores the hormones of the posterior pituitary (ADH, oxytocin), as well as releases hormones that influence the anterior pituitary and *its* hormones. Each of the five cell types in the anterior pituitary corresponds to one of five effector organs. The hypothalamus releases five hormones, each one specific to one of the five cell types in the anterior pituitary. Each cell type releases one of five hormones, each of which affects one of five effector organs. Each of those effector organs, in turn, releases its own unique hormone that has systemic effects. Each story begins in the Pituitary series but finishes out in the series of the corresponding effector organ.

The **thyroid gland** makes thyroid hormone. It is specialized to do only that. It is a clean example of a hypothalamic-pituitary axis. The hypothalamus makes one hormone; the anterior pituitary makes one hormone; the thyroid gland makes one hormone. The thyroid gland makes only thyroid hormone. No overlap, no additional regulation. The normal thyroid gland, functional disorders of the thyroid, and structural diseases (i.e., cancer) of the thyroid are discussed in the Thyroid series.

The **adrenal glands** make cortisol in response to anterior pituitary hormones. But the adrenal glands also make aldosterone in response to angiotensin 2, weak androgens, and epinephrine. The adrenal medulla is more an extension of the sympathetic nervous system than it is an endocrine gland. This overlap of function and regulation makes it challenging for the human brain—there isn't a neat separation of endocrine functions. There is a hypothalamic-pituitary-adrenal axis, but there is also the renin-angiotensin-aldosterone system and autonomic innervation. The adrenal glands are discussed in the Adrenal series.

The **growth hormone axis** uses the liver as its endocrine gland. The liver does a lot of things—unlike most of the endocrine glands—and one of its roles is to make the effector molecule downstream of growth hormone. So although we will use the liver as an "endocrine gland" in this axis, it doesn't fit so neatly as the thyroid gland does.

The **prolactin axis** isn't an axis at all. Prolactin release from the anterior pituitary results in breast milk production rather than in an effector hormone. We will discuss growth hormone and prolactin in the context of the anterior pituitary in Pituitary #2: *The Unhealthy Anterior Pituitary*.

The **gonads** make sex hormones. Although there is a hypothalamic-pituitary-gonad axis, it is discussed in the Reproduction module and not in this Endocrine module.

Then there are two endocrine glands out of reach of the hypothalamus and anterior pituitary.

The **parathyroid glands** manage calcium homeostasis. Calcium homeostasis is intimately intertwined with bone homeostasis because over 98% of the body's calcium is stored in mineralized bone. The lessons in the Parathyroid gland series take care to keep bone separate from calcium, to show you that there are calcium disorders that have consequences for bone and also bone disorders that have consequences for calcium.

The **endocrine pancreas** is outside the regulation of the hypothalamus and pituitary. You have already spent almost twenty lessons studying the endocrine pancreas in Metabolism. In those lessons, we studied the effects of insulin and glucagon from the perspective of metabolic pathways, gene transcription, and cytoplasmic regulation. In these lessons, we now re-explore those concepts from the perspective of the hormones and the cells they affect. In the Pancreas series, the main emphasis will be on diabetes and diabetes management, but we do explore other endocrine functions, such as those of glucagon and somatostatin.

Endocrine Signaling

We discussed endocrine signaling in Gen Phys and Gen Pharm. One cell releases a hormone into the blood, and another cell receives that signal. This is long-distance communication at its finest. A cell releases a compound into the bloodstream, and, like a drug, that compound is distributed throughout the body. All cells are exposed to that compound. Only a few cell types—sometimes only one—can hear that message.

In endocrine signaling, there are only a few things that can go wrong. Everything comes down to either too much or too little hormone.

1. The message is not sent. Each gland releases a hormone. If the gland is diseased, the hormone cannot be released. If the signal is never sent, the target may be healthy and well, but it doesn't matter. Until the signal is sent, the signal cannot be heard. This produces a hormone deficiency.

2. The message is not received. Each gland releases a hormone, and each hormone has a receptor. If the cells with the receptor are lost or that receptor is damaged, it doesn't matter if the signal is sent; the intended target cannot hear it. This also produces hormone deficiency.

3. Excess message is sent. If there is ever too much signal, whether from exogenous administration, endogenous production, or malignancy, there will be excess production of the hormone.

Hormones come in all shapes and sizes and utilize all sorts of receptors. The next section catalogs them for you. We aren't going to rehash them here, but if you need a refresher in hormone signaling, take a look at either General Physiology #5: *Receptors* or General Pharmacology #7: *Receptors and Second Messengers*. We're going to talk receptor tyrosine kinase, G protein-coupled receptors (G_i, G_s, and G_q), cytoplasmic receptors, and nuclear receptors.

Cataloging Endocrine Signaling

Do not, under any circumstances, attempt to memorize these tables. There are patterns, but they are too involved to be helpful. For example, the chemical structures of prolactin and growth hormone are similar, and they both use a receptor tyrosine kinase that uses the JAK2 pathway. Another example is that thyroid hormone's and sex hormone's axes show G_q-G_s-cytoplasmic receptor flow. But there are so few of these patterns that are obvious and without a teleologic reason behind them that it becomes superfluous to

try. Amine hormones are stored in vesicles, and so require calcium influx in order to be released. But any receptor activation could have downstream calcium effects, even though we teach G_q as the G_q-IP_3-Ca^{2+} pathway. The point is, don't learn from this table. But do use the table as you move through the module. Don't let these details hold you up. We spent the time to build these tables, so you don't have to.

These tables were made for reference. The first is categorized so that the second hormones that use the same second messenger system are placed next to each other, and the axes divided hypothalamus, anterior pituitary, target organ. It also includes hormones that are outside the HPA axis, such as aldosterone and parathyroid hormone. The second table is the HPA hormones only, organized in each axis. The third table is organized by second messenger, without respect to the geographic location of the hormone's activity.

HORMONE	MADE BY	TARGET	TYPE	SECOND MESSENGER
ORIGIN SIGNAL				
CRH	Hypothalamus	Anterior pituitary	Amine	G_s-AC-cAMP-PKA
GHRH	Hypothalamus	Anterior pituitary	Amine	G_s-AC-cAMP-PKA
Somatostatin	Hypothalamus	Anterior pituitary	Amine	G_i-AC-cAMP-PKA
TRH	Hypothalamus	Anterior pituitary	Amine	G_q-IP_3-Ca^{2+}
GnRH	Hypothalamus	Anterior pituitary	Amine	G_q-IP_3-Ca^{2+}
Dopamine	Hypothalamus	Anterior pituitary	Amine	N/A
*Renin	JG apparatus	RAAS cascade	N/A	N/A
MIDDLEMAN				
Prolactin	Anterior pituitary	Breast	Amine	RTK—JAK2
GH	Anterior pituitary	Liver	Amine	RTK—JAK2
TSH	Anterior pituitary	Thyroid	Amine	G_s-AC-cAMP-PKA
LSH/FH	Anterior pituitary	Gonads	Amine	G_s-AC-cAMP-PKA
ACTH	Anterior pituitary	Adrenal gland	Amine	G_s-AC-cAMP-PKA
*Angiotensin 2	RAAS cascade	Adrenal gland	Amine	G_q-IP_3-Ca^{2+}
EFFECTOR ORGANS				
IGF-1	Liver	All cells	Amine	RTK—JAK2
Catecholamines	Adrenal medulla	Endothelial cells	Amine	G_s-cAMP-PKA G_q-IP_3-Ca^{2+}
Cortisol	Adrenal cortex	All cells	Steroid	Cytoplasmic receptor
Aldosterone	Adrenal cortex	Collecting duct	Steroid	Cytoplasmic receptor
Thyroid hormone	Thyroid gland	All cells	Steroid	Nuclear receptor
INDEPENDENT HORMONES				
Calcium	N/A	Parathyroid gland	N/A	G_i-AC-cAMP-PKA G_q-IP_3-Ca^{2+}
Parathyroid hormone	Parathyroid gland	PCT DCT Osteoblasts	Amine	G_s-AC-cAMP-PKA G_q-IP_3-Ca^{2+}
Calcitonin	Thyroid gland (parafollicular)	Osteoclasts	Amine	G_s-AC-cAMP-PKA G_q-IP_3-Ca^{2+}
1,25-dihydroxyvitamin D	Kidney	Enterocytes	Lipid	Nuclear receptor

Table 1.1

HORMONE	MADE BY	TARGET	TYPE	SECOND MESSENGER
CORTISOL				
CRH	Hypothalamus	Anterior pituitary	Amine	G_s-AC-cAMP-PKA
ACTH	Anterior pituitary	Adrenal gland	Amine	G_s-AC-cAMP-PKA
Cortisol	Adrenal cortex	All cells	Steroid	Cytoplasmic receptor
GROWTH HORMONE				
GHRH	Hypothalamus	Anterior pituitary	Amine	G_s-AC-cAMP-PKA
GH	Anterior pituitary	Liver	Amine	RTK—JAK2
IGF-1	Liver	All cells	Amine	RTK—JAK2
THYROID				
TRH	Hypothalamus	Anterior pituitary	Amine	G_q-IP_3-Ca^{2+}
TSH	Anterior pituitary	Thyroid	Amine	G_s-AC-cAMP-PKA
Thyroid hormone	Thyroid gland	All cells	Steroid	Nuclear receptor
SEX HORMONES				
GnRH	Hypothalamus	Anterior pituitary	Amine	G_q-IP_3-Ca^{2+}
LSH/FH	Anterior pituitary	Gonads	Amine	G_s-AC-cAMP-PKA
Testosterone Estrogen	Gonads	Everywhere	Steroid	Cytoplasmic receptor
PROLACTIN				
Dopamine	Hypothalamus	Anterior pituitary	Amine	N/A
Prolactin	Anterior pituitary	Breast	Amine	RTK—JAK2
Angiotensin 2	Kidney	Adrenal gland	Amine	G_q-IP_3-Ca^{2+}
Aldosterone	Adrenal cortex	Collecting duct	Steroid	Cytoplasmic receptor

Table 1.2

HORMONE	MADE BY	TARGET	TYPE	SECOND MESSENGER
CRH	Hypothalamus	Anterior pituitary	Amine	G_s-AC-cAMP-PKA
GHRH	Hypothalamus	Anterior pituitary	Amine	G_s-AC-cAMP-PKA
Somatostatin	Hypothalamus	Anterior pituitary	Amine	G_i-AC-cAMP-PKA
TSH	Anterior pituitary	Thyroid	Amine	G_s-AC-cAMP-PKA
LSH/FH	Anterior pituitary	Gonads	Amine	G_s-AC-cAMP-PKA
ACTH	Anterior pituitary	Adrenal gland	Amine	G_s-AC-cAMP-PKA
TRH	Hypothalamus	Anterior pituitary	Amine	G_q-IP_3-Ca^{2+}
GnRH	Hypothalamus	Anterior pituitary	Amine	G_q-IP_3-Ca^{2+}
Angiotensin 2	Kidney	Adrenal gland	Amine	G_q-IP_3-Ca^{2+}
Prolactin	Anterior pituitary	Breast	Amine	RTK—JAK2
GH	Anterior pituitary	Liver	Amine	RTK—JAK2
IGF-1	Liver	All cells	Amine	RTK—JAK2
Dopamine	Hypothalamus	Anterior pituitary	Amine	N/A
Cortisol	Adrenal cortex	All cells	Steroid	Cytoplasmic receptor
Aldosterone	Adrenal cortex	Collecting duct	Steroid	Cytoplasmic receptor
Sex hormones	Gonads	Everywhere	Steroid	Cytoplasmic receptor
Thyroid hormone	Thyroid gland	All cells	Steroid	Nuclear receptor
1,25-Dihydroxyvitamin D	Kidney	Enterocytes	Lipid	Nuclear receptor
Catecholamines	Adrenal medulla	Endothelial cells	Amine	G_s-cAMP-PKA and G_q-IP_3-Ca^{2+}
Parathyroid hormone	Parathyroid gland	PCT DCT Osteoblasts	Amine	G_s-AC-cAMP-PKA and G_q-IP_3-Ca^{2+}
Calcitonin	Thyroid gland (parafollicular)	Osteoclasts	Amine	G_s-AC-cAMP-PKA and G_q-IP_3-Ca^{2+}

Table 1.3